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Cross-comparison of cancer drug approvals at three international regulatory agencies

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ABSTRACT

Background The primary objective of the present study was to examine the drug approval process and the time to approval (TTA) for cancer drugs by 3 major international regulatory bodies—Health Canada, the U.S. Food and Drug Administration (FDA), and the European Medicines Agency (EMA)—and to explore differences in the drug approval processes that might contribute to any disparities.

Methods The publicly available Health Canada Drug Product Database was surveyed for all marketed antineoplastic agents approved between 1 January 2005 and 1 June 2013. For the resulting set of cancer drugs, public records of sponsor submission and approval dates by Health Canada, the FDA, and the EMA were obtained.

Results Overall, the TTA for the 37 antineoplastic agents that met the study criteria was significantly less for the FDA than for the EMA ($\bar{X}$ = 6.7 months, $p < 0.001$) or for Health Canada ($\bar{X}$ = 6.4 months, $p < 0.001$). The TTA was not significantly different for Health Canada and the EMA ($\bar{X}$ = 0.65 months, $p = 0.89$). An analysis of the review processes demonstrated that the primary reason for the identified discrepancies in TTA was the disparate use of accelerated approval mechanisms.

Summary In the present study, we systematically compared cancer drug approvals at 3 international regulatory bodies. The differences in TTA reflect several important considerations in the regulatory framework of cancer drug approvals. Those findings warrant an enhanced dialogue between clinicians and government agencies to understand opportunities and challenges in the current approval processes and to work toward balancing drug safety with timely access.

Key Words Drug approval processes, cancer drugs, Health Canada, FDA, EMA

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INTRODUCTION

With the recent evolution of cancer therapy paradigms from pan-cytotoxic therapies toward targeted agents, treatment outcomes for cancer patients have been expected to improve. However, the rate of molecular and genomic advancement in cancer research appears to outpace the processes of regulatory bodies to make new therapies available to patients[1]. Consequently, a salient aspect of cancer drug access is timely approval of drugs that have the potential to improve the clinical course of disease.

Previous studies have demonstrated that differences in outcomes of approval processes by regulatory bodies result in clinically relevant disparities in drug access on an international scale[2]. The relative pace of drug approvals across the 3 main regulatory bodies—Health Canada, the U.S. Food and Drug Administration (FDA), and the European Medicines Agency (EMA)—can be attributed to a multitude of factors, including specific priorities of the agencies and complexities in regional legislation and processes, among other considerations. However, predictors of regulatory outcomes have not yet been identified. Accordingly, in the present study, we performed the first drug-by-drug analysis of cancer drug approvals by those regulatory bodies, and we dissect the major factors contributing to international disparities in drug approval times.

METHODS

The publicly available Health Canada Drug Product Database (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php) was surveyed for all marketed therapies with the class designation "antineoplastics" approved between 1 January 2005 and 1 June 2013. For the 37 new antineoplastic agents that met the study criteria, the approval dates and the original submission filing dates

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were extracted from the Summary Basis of Decision documents issued by Health Canada, where available. Similar data about submission and approval dates for the same drugs were obtained for the FDA from public FDA approval letters and from the EMA's Authorization Details and the European Public Assessment Report for each drug. Dates of submission and approval include only the first indication for which the drug was approved and not supplemental submissions or additional approvals. Only active treatment drugs were surveyed and not drugs related to supportive oncology care.

In the statistical analyses, 2-tailed t-tests were used to compare the time to drug approval between two agencies; analysis of variance was used for comparisons involving all 3 agencies.

RESULTS

To facilitate this comparative analysis of times from initial drug submission to approval by each regulatory agency, the period from the filing of a submission by a sponsor until the approval for marketing was granted was evaluated. On average, the time to approval (TTA) is approximately 14.0 months for Health Canada and 14.2 months for the EMA; it is 6.9 months for the FDA (Tables I and II).

Of the identified drugs assessed by all 3 agencies, cabazitaxel had the shortest TTA: only 17 days at the FDA. The FDA approved cabazitaxel for use in combination with prednisone for the treatment of patients with metastatic hormone-refractory prostate cancer previously treated with a docetaxel-containing regimen. Cabazitaxel was reviewed under the FDA's priority review program, designed to expedite the review process for drugs that might offer breakthroughs in treatment (FDA press announcement, 17 June 2010). In Canada and Europe, the TTA for cabazitaxel was just under 1 year (11.63 and 11.03 months respectively).

The overall TTA for the drugs analyzed in the present study was significantly less at the FDA than at Health Canada ($\bar{X}$ = 6.4 months, $p < 0.001$); the overall TTA at Health Canada and at the EMA did not significantly differ ($\bar{X}$ = 0.65 months, $p = 0.89$; Figure 1). As anticipated, the overall TTA was also significantly less for the FDA than for the EMA ($\bar{X}$ = 6.7 months, $p < 0.001$; Figure 1).

It is important to note that, in some instances, approval data were available only for 1 or 2 of the agencies. Differences in TTAs were calculated only for drugs that were reviewed by all 3 agencies. Importantly, of the drugs surveyed, 30 of 37 underwent an expedited approval at the FDA (Table III). The differences in drug approvals identified here might therefore be largely related to the disparate use of accelerated drug approval mechanisms by the 3 regulatory agencies. However, the median TTAs for the 7 drugs that did not undergo priority review at the FDA were still lower than the median TTAs for the same drugs at Health Canada and the EMA (median: 10.1 months FDA, 17.7 months Health Canada, and 15.5 months EMA).

Finally, drugs are often filed for FDA review before they are submitted for approval at Health Canada or the EMA (Table IV). The mean time from FDA submission to submission at an additional regulatory body was 28.4 months for Health Canada and 12.9 months for the EMA.

TABLE I Parameters derived from a comparison of the time from an initial drug submission by a pharmaceutical company to the date of approval for marketing in months, by regulatory body

Parameter	Time to approval (months)		
	Health Canada	FDA	EMA
Average	14.0	6.9	14.2
Median	11.7	6.1	13.9
Standard deviation	7.5	2.8	3.6
Range	2.87–39.33	0.57–13.2	4.93–22.37
p Value[a] (vs. FDA)	**6.5^{-7}**	—	**1.7^{-15}**
p Value (vs. EMA)	NS (0.89)		—

[a] Values in boldface type are statistically significant by two-tailed t-test.
NS = nonsignificant.

TABLE III U.S. Food and Drug Administration priority review drugs

Active ingredient
Abiraterone
Azacytidine
Bendamustine
Bevacizumab
Bortezomib
Brentuximab vedotin
Cabazitaxel
Cetuximab
Clofarabine
Crizotinib
Dasatinib
Enzalutamide
Eribulin
Erlotinib
Everolimus
Ibritumomab tiuxetan ^{90}Y
Ipilimumab
Lapatinib
Lenalidomide
Nelarabine
Ofatumumab
Oxaliplatin
Panitumumab
Regorafenib
Sorafenib
Sunitinib
Temsirolimus
Vandetanib
Vemurafenib
Vorinostat

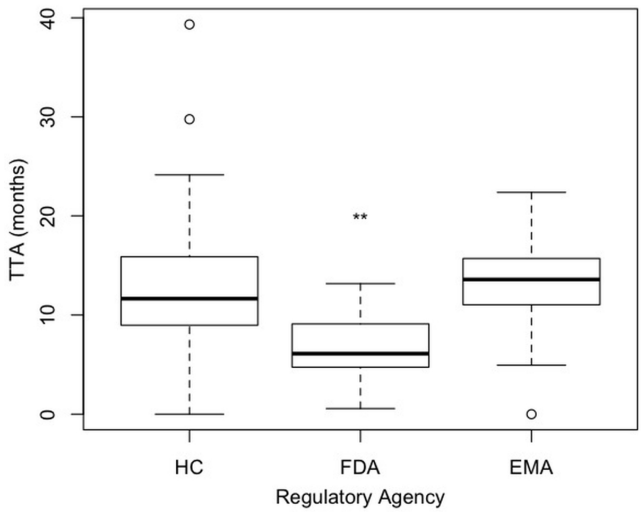

FIGURE 1 Spectrum of drug approval times at the U.S. Food and Drug Administration (FDA), Health Canada (HC), and the European Medicines Agency (EMA). Each box on the horizontal axis represents the set of times to approval (TTAs) for all drugs surveyed in the present study. The vertical axis depicts the TTA in months. Horizontal bars in each box correspond to the median TTA for the respective agency. Circles outside the box and the whiskers of each box plot denote outliers that are not within the 95th percentile of the other values in the dataset. **Statistically significant difference in TTA between the FDA and HC, and between the FDA and the EMA ($p < 0.001$).

DISCUSSION

The present study highlights variation in the processes involved in new oncology drug submissions to the main regulatory agencies and differences in the TTAs subsequently observed, to which use of expedited drug approvals might be the most significant contributor. Close examination of differences between the regulatory frameworks can provide insight into the varying drug approval times identified in the present study and in previous literature. Consistent with the findings in the present study, a previous report of the regulatory review of novel therapeutics by Health Canada, the EMA, and the FDA also noted that, on average, drug applications are reviewed more quickly by the FDA than by the EMA or Health Canada[3]. The findings in the present study are also consistent with other reports indicating that access to new cancer drugs is associated with greater use of expedited review procedures in the United States than in Europe[4,5].

Before accelerated approval mechanisms can be implemented in a meaningful way, a number of issues have to be addressed, including data quality, completeness, and clear guidelines for post-marketing surveillance of drugs approved through such pathways[6]. In the present study, the drug with the shortest TTA was cabazitaxel. The time from final sponsor submission to FDA approval was only 17 days. On closer inspection, that TTA was a consequence of the FDA's rolling review of the application, meaning that the sponsor was permitted to submit data to the FDA as it gradually accumulated during the development process[7]. The application for cabazitaxel was eventually approved on the basis of one randomized open-label trial of 755 patients, which demonstrated an overall survival advantage of 2.4 months and also reported cabazitaxel-associated deaths. The approval was contingent on the requirement of the sponsor to complete 6 essential post-marketing studies pertaining to sustained demonstration of efficacy, pharmacokinetics, safety, and toxicity.

Although expedient drug approvals are needed to deliver drugs to patients sooner, it is essential to balance the approval pace with assurance that the drugs are sufficiently safe. After accelerated approvals, the FDA has demonstrated a much higher than expected rate of label revision, suggesting that the rigour of the process has to be revisited[8]. Additionally, one thorough report of accelerated approval of cancer drugs by the FDA demonstrated that post-approval black-box warnings were added to the labels of 4 oncology drugs (17%) that received accelerated approval and 2 oncology drugs (9%) that received regular approval[9]. Recognizing that the FDA should raise its standards for granting accelerated approval to experimental cancer drugs, the Oncologic Drugs Advisory Committee in 2011 reached a consensus that the FDA must, for more definitive demonstration of efficacy, require that at least 2 controlled trials be actively under way[10].

In an effort to improve patient outcomes, concern about safety standards should not be dissipated. It is clear that vigilance in ascertaining clinical benefit in post-marketing studies is an essential cornerstone of successful accelerated approval processes[11].

Limitations

Some limitations of our study should be noted. First, the analysis was not designed to identify cancer drugs that were not approved in Canada, perhaps for valid reasons. For example, ponatinib, which was approved by the FDA in December 2012 through priority review and by the EMA in July 2013, has not yet been approved by Health Canada. Another salient consideration not addressed in the study is the fact that approval times are not the only dimension to drug access. Regulation of drug costs and coverage on regional levels constitute another important aspect of cancer drug access.

SUMMARY

Understanding the pace of cancer drug approvals, as well as the underlying factors, is a necessary dimension of the continuum of cancer drug access. The findings of the present study contribute to the published evidence that ongoing monitoring and inquiry into international cancer drug approval times is essential. Faster drug approval times do not always translate into a direct path to safe therapies and drug access. A global discussion about the methods and criteria for fast-track approvals is needed. We anticipate that this cross-comparison of drug approval times in Canada, the United States, and Europe can enhance the existing dialogue between clinicians and government agencies to understand the deficiencies and strengths in the various approval models and to work toward improving them.

TABLE II Time-to-approval database

Active ingredient	Route of administration	Cancer type	Initial approved indication	Time to approval (days)		
				Health Canada	U.S. FDA	EMA
Abiraterone	Oral	Prostate cancer	in combination with prednisone for patients with castration-resistant metastatic disease who have received prior therapy using docetaxel	216	139	262
Axitinib	Oral	Renal cell carcinoma	Metastatic disease of clear cell histology after failure of prior systemic therapy with either a cytokine or sunitinib	380	288	503
Azacitidine	Subcutaneous	Intermediate-2 and high-risk myelodysplastic syndrome, acute myeloid leukemia	Adult patients not eligible for hematopoietic stem-cell transplantation	211	142	343
Bendamustine	Intravenous	Non-Hodgkin lymphoma Chronic lymphocytic leukemia	Relapsed indolent disease that did not respond to, or that progressed after, rituximab therapy Symptomatic disease in patients who have not received prior therapy	351	305	148
Bevacizumab	Intravenous	Colorectal cancer	In combination with fluoropyrimidine-based therapy as first-line treatment in metastatic disease	591	153	405
Bortezomib	Intravenous	Multiple myeloma	Patients who have relapsed after front-line therapy, are refractory to their most recent therapy, and have recently undergone or are unsuitable for stem-cell transplantation	332	112	451
Brentuximab vedotin	Intravenous	Hodgkin lymphoma, systemic anaplastic large-cell lymphoma	After failure of autologous stem-cell transplantation or failure of at least 2 multi-agent chemotherapy regimens;	296	172	513
Cabazitaxel	Intravenous	Prostate cancer	In patients with castration-resistant (hormone refractory) metastatic disease previously treated with a docetaxel-containing regimen	349	17	331
Cetuximab	Intravenous	Colorectal cancer	In combination with irinotecan for the treatment of patients with EGFR-expressing metastatic disease who are refractory to other irinotecan-based regimens	655	31	364
Clofarabine	Intravenous	Acute lymphoblastic leukemia	Pediatric patients (1–21 years of age) with relapsed or refractory disease after at least 2 prior regimens	434	274	671
Crizotinib	Oral	Non-small-cell lung cancer	*ALK*-positive advanced or metastatic disease	322	149	454
Dasatinib	Oral	Chronic myeloid leukemia	Chronic-, accelerated-, or blast-phase disease with resistance or intolerance to prior therapy, including imatinib	362	182	312
Degarelix	Subcutaneous	Prostate cancer	For testosterone suppression in patients with advanced hormone-dependent disease in whom androgen-deprivation is warranted	532	299	356
Enzalutamide	Oral	Prostate cancer	Metastatic castration-resistant disease	86	101	360
Eribulin	Intravenous	Breast cancer	Metastatic disease in patients who have previously received 2 other regimens for metastatic disease. Prior therapy should have included an anthracycline and a taxane administered in either the adjuvant or metastatic setting	348	230	352
Erlotinib	Oral	Non-small-cell lung cancer	Monotherapy for locally advanced or metastatic disease after failure of at least 1 prior chemotherapy regimen when EGFR expression status is positive or unknown	255	112	389

TABLE II Continued

Active ingredient	Route of administration	Cancer type	Initial approved indication	Time to approval (days)		
				Health Canada	U.S. FDA	EMA
Everolimus	Oral	Renal cell carcinoma, astrocytoma	Metastatic disease after failure of either sunitinib or sorafenib (a NOC/c was later issued for use in patients 3 years of age or older with sub-ependymal giant-cell astrocytoma who are not candidates for surgery)	409	273	398 406
Histrelin	Subcutaneous	Prostate cancer	Palliative treatment of advanced hormone-dependent disease	616	305	620
Ibritumomab tiuxetan ^{90}Y	Intravenous	Non-Hodgkin lymphoma	Relapsed low-grade disease	1180	133	315
Ipilimumab	Intravenous	Melanoma	Metastatic or unresectable disease in patients who have failed or do not tolerate other systemic therapy for advanced disease	476	273	434
Lapatinib	Oral	Breast cancer	In combination with capecitabine for HER2-positive advanced or metastatic disease (update in 2013 indicates that this regimen is less effective than trastuzumab-based regimens)	893	181	615
Lenalidomide	Oral	Myelodysplastic syndrome	Disease with 5q deletion	339	264	471
Nelarabine	Intravenous	T-cell acute lymphoblastic leukemia, T-cell lymphoblastic lymphoma	When disease has not responded or has relapsed after treatment with at least 2 chemotherapy regimens	724	182	453
Nilotinib	Oral	Chronic myeloid leukemia	Accelerated-phase Philadelphia chromosome–positive (Ph+) disease in adults resistant or tolerant to at least 1 prior therapy with imatinib (as of 9 June 2011 was also approved for the treatment of newly diagnosed Ph+ disease in chronic phase	644	395	410
Ofatumumab	Intravenous	Chronic lymphocytic leukemia	CD20-positive disease refractory to fludarabine and alemtuzumab	413	269	438
Oxaliplatin	Intravenous	Colorectal cancer	In combination with 5-fluorouracil and leucovorin for the treatment of metastatic disease	207	306	
Pazopanib	Oral	Renal cell carcinoma	Metastatic clear cell disease who have received no prior therapy or prior therapy with cytokines for metastatic disease	345	304	472
Pertuzumab	Intravenous	Breast cancer	HER2-positive disease in patients who have not received prior anti-HER2 therapy or chemotherapy; in combination with trastuzumab and docetaxel	269	185	459
Regorafenib	Oral	Colorectal cancer	Metastatic disease in patients who have been previously treated with fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, and an anti-VEGF therapy, and, if wild-type *KRAS*, with anti-EGFR therapy	208	153	,
Sorafenib	Oral	Renal cell carcinoma	Advanced disease	266	165	315
Sunitinib	Oral	Gastrointestinal stromal tumour	After failure of imatinib because of resistance or intolerance	248	169	323
Temsirolimus	Intravenous	Renal cell carcinoma	Metastatic disease	396	237	410
Tositumomab and ^{131}I–tositumomab	Intravenous	Non-Hodgkin lymphoma	Low-grade CD20-positive relapsed or refractory, follicular or transformed disease, including in patients refractory to rituximab		825	
Trabectedin	Intravenous	Ovarian cancer Sarcoma	In combination with pegylated liposomal doxorubicin hydrochloride in patients with platinum-sensitive disease			417

TABLE II Continued

Active ingredient	Route of administration	Cancer type	Initial approved indication	Time to approval (days)	
				Health Canada	U.S. FDA	EMA
Vandetanib	Oral	Thyroid cancer	Symptomatic or progressive medullary disease unresectable locally advanced or metastatic disease	350	273	534
Vemurafenib	Oral	Melanoma	Unresectable *BRAF* V600–positive metastatic disease	212	111	289
Vorinostat	Oral	Cutaneous T-cell lymphoma	Cutaneous manifestations in patients with advanced disease	349	184	

FDA = Food and Drug Administration; EMA = European medicines Agency; NOC/c = Notice of Compliance with conditions; HER2 = human epidermal growth factor receptor 2.

TABLE IV Time in months between submissions made by the U.S. Food and Drug Administration (FDA) and submissions made by Health Canada and the European Medicines Agency (EMA)

Active ingredient	Submission date			Time between submissions	
	Health Canada	FDA	EMA	FDA vs. Health Canada	FDA vs. EMA
Abiraterone	23 Dec 2010	10 Dec 2010	17 Dec 2010	1.08	0.58
Alemtuzumab	1 Nov 2001	22 Dec 1999	23 Mar 2000	56.67	7.67
Axitinib	28 Jun 2011	14 Apr 2011	19 Apr 2011	6.25	0.42
Azacytidine	26 Mar 2009	29 Dec 2003	9 Jan 2008	159.50	122.67
Bendamustine	8 Sep 2011	31 Dec 2007	22 Oct 2009	112.25	55.08
Bevacizumab	27 Jan 2004	26 Sep 2003	4 Dec 2003	10.25	5.75
Bortezomib	1 Mar 2004	21 Jan 2003	31 Jan 2003	33.75	0.83
Brentuximab vedotin	11 Apr 2012	28 Feb 2011	31 May 2011	34.00	7.67
Cabazitaxel	2 Jul 2010	31 May 2010	20 Apr 2010	2.67	–3.42
Cetuximab	24 Nov 2003	24 Jan 2004	1 Jul 2003	–5.08	–17.25
Clofarabine	8 May 2008	29 Mar 2004	27 Jul 2004	125.08	10.00
Crizotinib	8 Jun 2011	30 Mar 2011	27 Jul 2011	5.83	9.92
Dabrafenib	31 Jul 2012	29 Jul 2012	24 Jul 2012	0.17	–0.42
Dasatinib	29 Mar 2006	28 Dec 2005	12 Jan 2006	7.58	1.25
Degarelix	2 Jun 2008	29 Feb 2008	27 Feb 2008	7.83	–0.17
Enzalutamide	4 Mar 2013	22 May 2012	26 Jun 2012	23.83	2.92
Eribulin	31 Dec 2010	30 Mar 2010	30 Mar 2010	23.00	0.00
Erlotinib	25 Oct 2004	29 Jul 2004	26 Aug 2004	7.33	2.33
Everolimus	31 Oct 2008	30 Jun 2008	1 Jul 2008	10.25	0.08
Histrelin	2 Jul 2004	12 Dec 2003	17 Nov 2005	16.92	58.83
Ibritumomab tiuxetan ^{90}Y	15 Feb 2002	9 Oct 2001	7 Mar 2003	10.75	42.83
Ipilimumab	13 Oct 2010	25 Jun 2010	5 May 2010	9.17	–4.25
Lapatinib	4 Dec 2006	13 Sep 2006	4 Oct 2006	6.83	1.75
Lenalidomide	12 Feb 2007	7 Apr 2005	28 Feb 2006	56.33	27.25
Nelarabine	28 Sep 2005	29 Apr 2005	26 May 2006	12.67	32.67
Nilotinib	5 Dec 2006	29 Sep 2006	5 Oct 2006	5.58	0.50
Ofatumumab	21 Jan 2011	30 Jan 2009	5 Feb 2009	60.08	0.50
Panitumumab	28 Apr 2006	12 May 2006	28 Apr 2006	–1.17	–1.17
Pazopanib	16 Jun 2009	19 Dec 2008	27 Feb 2009	14.92	5.83
Pertuzumab	31 Aug 2012	6 Dec 2011	1 Dec 2011	22.42	–0.42
Regorafenib	15 Aug 2012	27 Apr 2012	3 May 2012	9.17	0.50
Sorafenib	4 Nov 2005	8 Jul 2005	7 Sep 2005	9.92	5.08
Sunitinib	20 Sep 2005	10 Aug 2005	30 Aug 2005	3.42	1.67
Temsirolimus	20 Nov 2006	5 Oct 2006	5 Oct 2006	3.83	0.00
Thalidomide	19 May 2009	22 Dec 2003	22 Jan 2007	164.58	93.92
Vandetanib	27 Jan 2011	7 Jul 2010	1 Sep 2010	17.00	4.67
Vemurafenib	18 Jul 2011	28 Apr 2011	4 May 2011	6.75	0.50
MEDIAN				10.25	1.67
MEDIAN				28.42	12.88
RANGE				–5.08 to 1.6458	–17.25 to 122.67

CONFLICT OF INTEREST DISCLOSURES
We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: SV has served on advisory boards for Amgen, AstraZeneca, Boehringer Ingelheim, Bristol–Myers Squibb, Merck, Novartis, Pfizer, Roche, and Spectrum Health. NS has no conflicts to declare.

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